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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,995	09/29/2000	Ravi V. J. Chari	104322.198 US1	2588

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	PAPER NUMBER
1642	18

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/671,995	CHARI, RAVI V. J.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32,40,41 and 44-89* is/are pending in the application.

4a) Of the above claim(s) *1-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,41 and 44-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-32,40,41 and 44-89* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The amendment filed August 23, 2002 in Paper No. 17 is acknowledged and has been entered. Claims 50-53 and 72-75 have been amended.

2. Receipt of the declaration filed August 23, 2002 as part of Paper No. 17 is acknowledged.

3. Claims 1-32, 40, 41, and 44-89 are pending in the application. Claims 1-32 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper Nos. 13 and 14.

4. Claims 40, 41, and 44-89 are currently under prosecution.

Grounds of Claim Rejections Withdrawn

5. Unless specifically reiterated below, the grounds of claim rejections set forth in the previous Office action mailed May 24, 2002 (Paper No. 16) have been withdrawn.

Grounds of Claim Rejections Maintained and Reply to Applicants' Remarks

Claim Rejections - 35 USC § 112

6. The specification is objected to and claims 52 and 74 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or

(3) deposited for the reasons set forth in the previous Office action mailed May 24, 2002 (Paper No. 16).

Applicant has traversed these grounds of rejection. Applicants' arguments have been carefully considered but not found persuasive for the reasons set forth in the previous Office action. Although Applicant has argued that monoclonal antibodies C242 and N901 are known in the art and could be produced without undue experimentation, provided one has assess to the hybridoma producing said antibodies, MPEP § 2401.01 states to avoid the need for a deposit, biological materials must be known and readily available – *neither concept alone suffices*.

Although Applicant has remarked, "a hybridoma cell line having use in the invention and producing a C242 antibody was deposited by an entity unrelated to the present inventor at the European Collection of Animal Cell Cultures (ECACC) in the United Kingdom" (page 3, paragraph 2), Applicant has failed to make of record any of the facts and circumstances surrounding the access to the biological materials from said depository. The fact that Applicant and other members of the public were able to obtain the materials in question from a given depository and that reference to the material or a deposit thereof has been made in various publications prior to and after the filing date of the application does not establish the upon issuance of a patent on the application that such material would continue to be accessible to the public.

Applicant's remark that US Patent No. 5,552,293-A notes the deposit of the hybridoma cell line producing "a C242 antibody" is noted. However, MPEP § 2404.01 states:

> The mere reference to a deposit or the biological material itself in any document or publication does not necessarily mean that the deposited biological material is readily available. Even a deposit made under the Budapest Treaty and referenced in a United States or foreign patent document would not necessarily meet the test for known and readily available unless the deposit was made under conditions that are consistent with those specified in these rules, including the provision that requires, with one possible exception (37 CFR 1.808(b)), that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent. Ex parte Hildebrand, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990).

Applicant has not provided the required assurance that said depository would allow unlimited access to the material upon the issue of a patent upon this application. In the absence of evidence that the hybridoma producing monoclonal antibodies N901 and C242 are readily available to the public and that all restrictions imposed by the depositor, or by other investigators on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, the rejection is properly maintained.

If Applicant can establish that hybridomas producing monoclonal antibodies C242 and N901 are known and readily available, the Office will accept the showing. However, it should be noted that Applicant will take the risk that the material may cease to be known and readily available; and such a defect cannot be cured by reissue after the grant of a patent.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 52 and 74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in the previous Office action mailed May 24, 2002 (Paper No. 16).

As stated in the previous Office action, claims 52 and 74 are indefinite because the claims use of the designations "N901" and "C242" as the sole means of identifying the humanized antibodies to which the claims refer. The use of laboratory designations only to identify a particular antibody renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct antibodies.

Applicant has traversed these grounds of rejection. Applicant's arguments have been carefully considered but not found persuasive for the reasons stated in the previous Office action and reiterated above. Applicant is required under 35 USC § 112, second paragraph to particularly point out and distinctly claim and the subject matter

that is regarded as the invention. To distinctly claim and particularly point out a specific biological material requires the use of a unique identifier, e.g., the recitation of the name of a particular depository and the number under which the deposit has been made; the recitation of the particular amino acid sequence of a polypeptide; the recitation of the particular polynucleotide sequence of a nucleic acid molecule.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 40, 41 and 44-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu, et al (*Proceedings of the National Academy of Sciences USA* **93**: 8618-8623, 1996; Form PTO-1449, citation K) in view of Mendelsohn (*Clinical Cancer Research* **3**: 2703-2707, 1997; Form PTO-1449, citation Y) and Hortobagyi (*Oncology* **11**: 11-15, 1997) for the reasons set forth in the previous Office action mailed May 24, 2002 (Paper No. 16).

Claims 41 and 66-89 are drawn to a kit comprising at least one chemotherapeutic agent and at least one immunoconjugate, wherein said immunoconjugate comprises a humanized antibody, namely C242 or N901, conjugated to an anti-mitotic agent. Claims 40 and 44-65 are drawn to a composition comprising a chemotherapeutic agent and further comprising an immunoconjugate, wherein said immunoconjugate comprises a humanized antibody, namely C242 or N901, conjugated to an anti-mitotic agent.

Applicant has traversed these grounds of rejection arguing that given the teachings of the prior art, it would not have been obvious to manufacture a kit comprising one chemotherapeutic agent and at least one immunoconjugate comprising a humanized antibody, namely C242 or N901, and an anti-mitotic agent, because there

would not have been any motivation to do so and the conclusion of obviousness is based upon improper hindsight reasoning. Additionally, Applicant has asserted that it would not have been obvious to combine a chemotherapeutic agent and an immunoconjugate comprising a humanized antibody, namely C242 or N901, and an anti-mitotic agent, because Liu, et al discloses that an immunoconjugate comprising a humanized antibody, namely C242, and a maystansinoid, namely DM1, is more effective alone than 5-flurouracil. Applicant has asserted that Liu, et al, thus, "teaches away" from the derivation of the claimed invention, a composition comprising at least one chemotherapeutic agent and at least one immunoconjugate, such as that disclosed by Liu, et al. Furthermore, Applicant has contended that the specification discloses unexpected results, as the observed additive or synergistic effects of the combination of chemotherapeutic agents was not expected by Applicant; and Applicant contends it would not have been expected by one of ordinary skill in the art at the time the invention was made.

In reply to Applicant's arguments, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Furthermore, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as kits were so highly prevalent in the art at the time the application was filed, the motivation to manufacture a kit comprising one chemotherapeutic agent and at least one immunoconjugate comprising a humanized antibody, namely C242 or N901, and an anti-mitotic agent would have been found in the knowledge generally available to one of ordinary skill in the art. Nevertheless, as the

previous Office action stated, given the teachings of Liu, et al, Mendelsohn, and Hortobagyi, one skilled in the art would have been motivated at the time the invention was made to manufacture the kit, because such a kit could be used to find effective combinations, strategies, and regimens, and to determine the optimal roles for one of the agents in relation to the others. In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In reply to Applicants' argument that it would not have obvious to manufacture a composition comprising a chemotherapeutic agent and the immunotoxin of Liu, et al, it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition that is to be used for the very same purpose. The idea of combining the first and second compositions to form a third flows logically from having the first and second been individually taught in the prior art. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980); see MPEP § 2144.06. The fact that Liu, et al teach that the second is more effective alone than the first alone would not have provided one with a reason not to combine the first and the second. Applicant's contention that additive or synergistic effects of combinations of anticancer agents would have been unexpected by one of ordinary skill in the art is baseless; nonetheless, both Mendelsohn and Hortobagyi teach combinations of anticancer agents and suggest a rationale for producing the combinations: the frequent observation of additive or synergistic effects. The other prior art, which was made of record in the previous Office action, also provides evidence that one skilled in the art at the time the invention was made would not have found any observed additive or synergistic effect of a combination of anticancer agents either surprising or unexpected.

Accordingly, Applicant's arguments have been carefully considered but not found persuasive. Therefore, the rejection of the claims under 35 USC § 103(a) for the reasons set forth in the previous Office action is maintained.

Conclusion

11. No claims are allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
November 7, 2002